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SUMMARY

Dosimetry for Epidemiological Studies: Learning from the Past, Looking to the Future

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INTRODUCTION

Assembling the suite of manuscripts for this special issue of *Radiation Research* has afforded us a unique opportunity to evaluate the various methods of dosimetry used in support of epidemiological studies as well as the strengths and weaknesses of different dosimetric approaches. Of equal importance is having the opportunity to highlight elements of dosimetry that are especially important to conducting convincing epidemiological studies.

In general, analytical epidemiological studies of radiation effects attempt to combine information on disease (e.g. cancer) occurrence with estimates of radiation dose to individuals such that the relationship between the increase in disease incidence compared to the background rate as a function of the true dose can be described. With regard to the language and science of dosimetry, there are a number of terms, assumptions and implied meanings that are often not clear to the variety of scientists involved in radiation epidemiology studies. This issue should help inform these researchers.

In this special issue of *Radiation Research* devoted to the dosimetric aspects of radiation epidemiology, we attempted to clarify what is meant by ''dosimetry for epidemiological studies'', what is required to ensure that the findings of dosimetry-based epidemiological studies are as credible and generalizable as possible, and to give practical examples from current or recent studies. While this collection of papers certainly does not cover all of the aspects of dosimetry in epidemiology, it is meant to describe where we have been in terms of applying dosimetry for epidemiological purposes and where we are going to further advance the discipline.

SUMMARY OF STUDIES PRESENTED

Readers of this issue of *Radiation Research* are probably already acquainted with a wide range of dosimetric methods. Here we briefly summarize the principal identifying components of the ten applications of dosimetric methods described in the individual papers. Table 1 contains a listing of the papers and a greatly abbreviated description of the methods employed and the available input data.

Medical Dosimetry

Methods for estimation of organ doses after the administration of radioisotopes as described by Brill *et al.* (*1*) are well developed and have depended for several decades on the formulations of the Medical Internal Radiation Dose (MIRD) Committee [see ref. (*2*) for a primer on those methods]. The basis for dose estimation by these methods is a metabolic model coupled with a *measured* amount of administered radioactive material. Unlike occupational and environmental dose estimations, the great advantage in these situations is that the amount of activity administered is usually known. Though the ability to accurately measure the administered activity does not pose any great technical challenges, differences between individuals in their metabolism (kinetics) and anatomy (size and exact location of organs) lead to uncertainties in the absorbed dose for any identified person. Thus, even when activity intake is known, doses cannot be estimated with absolute precision. One of the limitations in estimating individual dose arises from the use of standardized or mathematical phantoms that are assumed to representing the individual receiving the treatment dose.

Even iodine-131, one of the most studied nuclides for which kinetics in the human body has been described since the early 1950s (*3*), has dose uncertainties, partly because of human variation, but also due to secular changes in the dietary component of stable iodine. Changes in iodine intake have occurred at the local, national and international levels, and these can affect the amount of radioiodine absorbed by each individual thyroid gland.

Estimation of doses from medical procedures, including treatments and diagnostic procedures, as described by Stovall *et al.* (*4*), involves traditional treatment planning techniques, archival data collection, and contemporary mea-

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TABLE 1
Summary of Physical or Calculation-Based Dosimetric Methods Described in Publications of this Issue

Exposure category/authors	Exposure setting, population, and location	Organs/tissues for dose estimation	Mode of exposure (internal, external)	Primary methods and input data
Medical				
Brill *et al.* (*1*)	Clinical: patients (emphasis on U.S.)	Thyroid primarily	Internal (^{131}I)	Metabolic model using measured administered radionuclides
Stovall *et al.* (*4*)	Clinical: patients (emphasis on U.S.)	All organs + red bone marrow (RBM)	External and internal	Measurements and calculations based on records from administered treatments and/or diagnostic tests
Occupational				
Bouville *et al.* (*6*)	Reactor: clean-up workers (Ukraine)	RBM primarily, internal (minor)	External primarily, internal (minor)	Film badge measurements (individual or group), exposure rate, questionnaire responses
Gilbert *et al.* (*7*)	Various reactors: workers (U.S., Europe)	Whole-body	External primarily	Film badge and other dosimeter measurements
Simon *et al.* (*8*)	Clinical: radiologic technologists (U.S.)	All organs, emphasis on breast, skin, RBM	External	Film badge measurements, questionnaire responses, historical literature
Environmental				
Beck *et al.* (*9*)	Public: population living downwind of nuclear test sites (U.S., Kazakhstan, Marshall Islands)	Thyroid primarily, also RBM	External and internal	Measurements of exposure rate coupled with environmental transfer models, questionnaire responses
Cullings *et al.* (*12*)	Public: A-bomb survivors (Hiroshima and Nagasaki, Japan)	Whole-body	External	Reconstruction of detonation conditions (source term), geographic location, house construction
Degteva *et al.* (*11*)	Public: people living near contaminated river (Chelyabinsk, Russia)	All organs + RBM	External and internal	Release data and environmental transfer model
Likhtarev *et al.* (*10*)	Public: people living near Chernobyl reactor (Ukraine, Belarus)	Thyroid	External and internal	Measurements of ^{131}I in thyroid plus model
Puskin *et al.* (*15*)	Homes and mines (international)	Lung	Internal by inhalation	Physics based model to convert from exposure to dose, dependent on environmental measurements of ^{222}Rn

surements, sometimes of aged radiation-generating machines. The goal of those various techniques is, in general, to characterize the dose to organs/tissues outside of treatment areas, primarily due to within-body scatter of radiation and leakage from the treatment machine. Various types of phantoms are used for dose measurements and dose estimation, including mathematical, anthropometric and water phantoms. Therapy doses are particularly amenable to reconstruction because, much like when radiopharmaceuticals are administered, the irradiation conditions were controlled and the dose to the treatment site was recorded, although detailed radiation records are not always accessible (*5*). Since patients comprise the largest population group exposed to doses ranging from very low to extremely high, dosimetry and risk associated with those exposures will continue to be a major focus of study.

Occupational Dosimetry

Occupational exposure includes a wide range of job descriptions in the medical, weapons construction, and nuclear power industries, and dosimetric methods reflect those various conditions.

Dose estimation for the Chernobyl clean-up workers as described by Bouville *et al.* (*6*) took advantage of the unique exposure conditions that could be assumed as relatively homogeneous over the body. In that study, doses were estimated by one of four different methods, depending on the individual study subject and the data available for that subject: individual film badge measurements, a group film badge measurement, group assessment based on the dose rate at the work assignment location, or individual reconstruction based on time spent at different locations taking into account the respective dose rates at those locations. The doses for the Estonian workers were also estimated by biodosimetric methods, but neither GPA nor FISH was able to detect any biological changes compared to control subjects. The failure of biodosimetry to support estimated doses was likely related to the overestimation of recorded doses for those exposed workers as well as the

limits of detection. Nuclear workers, in the context of the paper by Gilbert *et al.* (*7*), include personnel involved in weapons production, nuclear power generation, and related research activities in the U.S., UK and Canada. Studies of those workers encountered some of the same problems as the study of radiological technologists (*8*) in that workers were monitored over time (from the 1940s through recent years) when the calibration methods for personnel monitoring badges were evolving. In addition to different types of calibrations, dosimeters used early in the profession did not respond accurately to all radiation energies or uniformly with direction. Gilbert and colleagues (*7*) primarily characterize the bias and uncertainties related to the dosimetry and describe some ways to account for the uncertainty so that dose–response analyses are not unnecessarily limited.

Radiation technologists began to be needed in the early part of the 20th century during the developmental period of diagnostic and therapeutic radiology. Throughout the 20th century, the responsibilities of these medical professionals changed from a mixture of all tasks in a radiology department to becoming more specialized in specific procedures. Over that same period, understanding and recognition of radiation risks, development of ALARA (as low as reasonably achievable) principles, and improved technologies served to reduce the doses per individual procedure to the patient and the technologist. At the same time, the workload of technologists has increased due to the widespread use of radiological procedures in medicine. Estimation of doses to medical workers rarely goes beyond a reported value of the personal dose equivalent, a regulatory quantity derived directly from a calibrated film badge. In the dosimetric methods described by Simon *et al.* (*8*), assumptions based on literature review were used to describe the nature and quality of radiation fields to which individual technologists were exposed, thus allowing for estimation of organ doses and their uncertainties. For reconstruction of doses to radiation technologists, responses to detailed questionnaires were used as well as large national databases of film badge readings that included data on members of the cohort.

Environmental Dosimetry

The estimation of doses from exposure to radioactive fallout from nuclear weapons tests and from releases of radionuclides to the environment occupies a special niche in dosimetric applications because it includes a wide variety of disciplines including physics, environmental science, anatomy and physiology, and even human behavior.

There are several unique qualities of fallout dosimetry. First was the large number of source terms; between 1945 and 1980, over 500 weapons tests were conducted in the atmosphere at a number of locations around the world. Another unique quality of fallout studies is that individual dosimetry data, except occasionally for military personnel, are never available. Even for military personnel, monitoring data would apply only to external exposures, and fallout dose estimation usually includes internal exposure as well. Hence dose estimation for fallout exposure almost always requires the use of complex models with numerous parameters. To characterize those parameters, only very limited amounts of real data are typically available, resulting in high uncertainty, particularly for internal dose. Second, the long interval since the exposures occurred has resulted in loss of some original data, although the sparse historical measurement data available are generally sufficient to estimate external exposure doses reasonably well. Reconstruction of internal doses from ingestion and inhalation of radionuclides is significantly more complex and is almost always more uncertain than for external dose estimation. Internal dose estimates are typically based on estimates of the ground deposition per unit area of specific radionuclides and subsequent transport of radionuclides through the food chain whereas, for external dose estimation, reconstruction is reasonably straightforward and relevant data in the form of exposure rates are often available.

In the description of fallout dosimetry methods by Beck *et al.* (*9*), the number of locations for which dose estimates has been made is impressive and covers most of the continents as well as some island locations. Moreover, because of the large numbers of measurements of fallout radionuclides in the environment and in humans, fallout studies have been some of the most innovative in terms of developing individual dose and uncertainty estimates.

Despite nearly 50 years of study, technical challenges in fallout dosimetry still remain. These include needed improvements in modeling of radionuclide fractionation with changes in distance and particle size, consistency of models between U.S., Russian and other investigators, and the continuing need to archive historical data that are at risk of permanent loss.

Individual thyroid doses from ^{131}I, as well as uncertainties, have been estimated for two cohort studies of approximately 13,000 Ukrainians and 12,000 Belarussians exposed to fallout from the Chernobyl accident. The study described by Likhtarev *et al.* (*10*) is unique in that few, if any, other studies of environmental exposure have been able to rely on measurements of activity in the thyroid of each study subject. The assessment of the individual thyroid doses from intakes of ^{131}I is based on the results of measurements of external γ radiation by means of radiation detectors placed against the neck. Within a few weeks after the Chernobyl accident, approximately 200,000 of those measurements were made in Belarus and 150,000 in Ukraine. In common with many other studies of exposure of the thyroid gland, the parameter that accounts for a large part of the uncertainty is the thyroid mass. However, unlike other studies, there was uncertainty in the determination of the ^{131}I content in the thyroid due to the direct γ-ray measurements and their interpretation.

Similar to Chernobyl, where doses were estimated to workers (*6*) and the public (*10*) living downwind of the

damaged reactor, reconstructed doses to populations living downstream from the Mayak reactor have also been estimated. The Techa River dosimetry system, as described by Degteva *et al.* (*11*), estimates dose to the population living along the river that received discharges from the Mayak facility. The Techa River dosimetry system was developed so that health risks of low to moderate dose rates could be evaluated in several exposed cohorts. In that dosimetry system, unique data on ^{90}Sr in teeth (assayed by surface β-particle activity), whole-body measurements, and autopsy measurements have been used for validation of estimated doses.

In the paper by Cullings *et al.* (*12*), we get an appreciation for the evolution of the dosimetry for A-bomb survivors from the first implementation, T57D, to the present system, DS02. More importantly, this paper clarifies that what was previously thought to be a substantial ''neutron discrepancy'' was actually not a major deficiency. The exercise of applying the latest nuclear weapons codes and other computationally intensive calculations, made feasible by continued improvements in computer speed, served to improve the estimates of explosive yield and height of burst and to increase the spatial and temporal resolution of the DS02 calculations over previous versions.

A-bomb survivor dosimetry is unique in many ways. First, there was a single acute exposure, a rare event except for some unintended criticality events, none of which are discussed in the papers here. The predominant difficulty in A-bomb survivor dosimetry has been to accurately describe the source term and the energy fluence and air kerma at the location of each survivor. No other dosimetry system used for an epidemiological study has had such stringent requirements. To arrive at the most recent dose estimates, hundreds of person-years of effort have been expended over a period of about 50 years. Most remaining issues requiring further study appear to be related to risk analyses, e.g., adjustments for dosimetry error, although the Nagasaki factory workers still appear to indicate a positive bias in their estimated doses.

Radon gas is believed to be a primary source of radiation risk to the public and has been the subject of information campaigns (see http://www.epa.gov/radon/pubs/), reports of well-respected committees (*13*, *14*), and countless studies, conference presentations, and letters to journal editors debating the degree of risk. It may come as a surprise to some readers that radon risk continues to be so hotly debated and that risk estimation has been based for decades on exposure (a measure of the α-particle energy released in air, integrated over time) rather than on absorbed dose delivered to tissue. Puskin *et al.* (*15*) discuss the labyrinth of issues related to lung dosimetry from radon progeny. Though the decay of radon gas through a series of radioactive by-products has been thoroughly understood for decades, the estimation of tissue dose has been one of the last issues resolved, partly because the short range of α-particle radiation complicates calculations, but also because the distribution of the radioactive progeny in the respiratory tract is far from uniform. In addition, it is widely known that the quality of air in mines, where most risk studies have been conducted, and in homes, where greater numbers of people are exposed, differs considerably. These differences inevitably have led to uncertainty in estimated doses from radon.

Looking to the Future

Here we discuss some specific challenges that became apparent during the review of the dosimetry applications presented in this issue. Meeting these challenges will serve to improve future epidemiological analyses by providing more precise organ dose estimates for individuals while eliminating bias and reducing dose misclassification.

Uncertainty

Understanding the uncertainty of models and estimated doses (*16*), minimizing uncertainly where possible and correcting dose–response relationships (*17*) for distortion of the dose response (i.e. the risk) in the presence of ''classical'' error will likely remain a challenge in all low-dose radiation studies. Whereas dosimetry papers typically represent a challenge for epidemiologists and biostatisticians to understand, physicists and dosimetrists meet similar difficulties in assimilating the concepts explained by Schaeffer and Gilbert (*18*) in their discussion on statistical implications of uncertainty. Readers will note the concerted attempt by those authors to provide a non-technical discussion, though the complexity of the issues can quickly be appreciated by trying to determine the degree to which any set of estimated doses contains classical or Berkson errors or combinations of the two. The additional problem of the lurking ''shared errors'' that result from complex estimation schemes and models, commonly used in dose reconstruction for environmental exposure scenarios, is discussed.

The possibility that either simpler or more complex exposure assessment models could be developed as a means to reduce dosimetric uncertainty has been considered. However, extremely complex models, while possibly justified as a means to understand physical processes, will not necessarily reduce uncertainty because of the additional parameters involved (*19*). Reviews of the reliability of the parameter values used in biokinetic and dosimetric models have been helpful in identifying the areas where improvements can be made (*20–22*).

Independent Verification of Estimated Doses

Within this issue of *Radiation Research*, there are at least ten methods described for estimating doses under different exposure scenarios or where different types of data are available. Radiation doses received by tissues of interest are not directly observable. Nor are data usually available to estimate tissue doses precisely except, perhaps, where dosimeters are placed *in situ* before an exposure takes place. Retrospective dose estimation, used extensively in

radiation epidemiology, has the distinct disadvantage that dose to the tissue of interest was almost never measured. With the exception of medical exposures, models are almost always employed to deduce the absorbed energy and the toolbox of techniques available for retrospective estimation typically have common weaknesses related to models and reliability of input data.

As a useful addition to the dosimetric toolbox, we have recently added the capability to make measurements of certain biological changes induced by radiation, i.e. biodosimetric measurements (*23, 24*). These measurements include, for example, fluorescence *in situ* hybridization for translocation analysis (using peripheral blood lymphocytes) and electron paramagnetic resonance (using tooth enamel). These techniques potentially allow for testing the reliability of estimated doses. There are limitations of the techniques themselves, including temporal stability, minimum detection limits, and sample collection. Verification of estimated doses, to the degree possible, will continue to be a necessary part of determining risks per unit dose whenever independent reliability is demanded.

The immediate challenge for biodosimetry is to develop alternative technologies that are less expensive and that can be implemented more quickly, are less biologically invasive, and have lower detection limits, while maintaining the signal many years after the exposure, as is currently possible for the FISH and EPR techniques. One current attempt is to develop *in vivo* EPR measurement methods that can be carried out without having to obtain extracted teeth. Innovations of this type would be useful, particularly to any moderate-sized epidemiological study that depended on retrospective dosimetry as well as being a useful tool after radiological terrorism events.

Other New Tools

The toolbox for estimating doses has long included various types of models. The set of tools that are available for dose estimation continues to expand, but the most basic set includes historical archived data, contemporary physical measurements to supplement historical data, models of transport phenomena, biokinetics, behaviors (e.g. food ingestion rates), and numerical simulation.

Due to advances in computer hardware as well as software implementation of complex algorithms, the application of simulation has expanded to cover nearly all aspects of dosimetry including environmental transport, energy and particle transport, and models of complex emission sources and complex-shaped receptors, e.g. the human body. Recently, voxel-based phantoms have seen a surge of development that will serve to improve the realism of dosimetric estimates. Voxels (meaning volume elements) are the three-dimensional equivalents of image pixels. Unlike mathematical phantoms that are equation-based descriptions of the geometry of the human body, voxel phantoms are based on computed tomographic or magnetic resonance images obtained from high-resolution scans of single individuals. Voxel phantoms consist of a huge number of volume elements (voxels) and are at the moment the most precise representation of the human anatomy (*25*). Studies of external doses to individuals, e.g. the study of radiation technologists (*8*), could take advantage of a new generation of phantoms and further individualize doses based on variations in individual morphology.

FINAL REMARKS

This review of the application of dosimetry in epidemiology has shown that for the most part, estimated doses can be usefully grouped by the exposure categories of medical, occupational and environmental. Moreover, those categories are generally indicative of the degree of uncertainty that should be expected in the estimated doses. Reconstruction of medically related doses will always have the advantage that irradiations were conducted under controlled conditions and that individual records are usually available for radiotherapy patients. This leads to the advantage of lower uncertainty of estimated doses and applies to both internal and external exposures. Dose received in an occupational setting would generally be less controlled than in medical settings, but the occupational environment often has monitoring data available, on either a group or individual level. Environmental exposures will almost always be the most uncertain and will require more complex models, particularly for estimating internal exposures. Moreover, the data available to reconstruct environmental exposures will generally be sparse compared to the other settings and will require more extensive use of interpolation and estimation strategies. However, past environmental exposure scenarios have an inherent importance because they represent the type of exposure that could affect the public in the future if accidents or radiological terrorism events occur.

There are several other conclusions to be drawn from this review. First, we believe that *organ absorbed dose*, reported in grays (Gy), and associated with information on the radiation quality, is the most relevant metric for epidemiological studies. Variations of *dose* involving the use of weighting factors, such as the *effective dose*, were devised for radiation protection purposes and not for scientific analyses. Those metrics of dose are confounded by regulatory weighting factors that are subject to change with time. Therefore, *equivalent dose* or *effective dose* does not have a place in epidemiology to elucidate radiation risk, where the most accurate possible estimates of absorbed doses are desired.

The movement within the epidemiology community to involve physicists/dosimetrists in radiation health effects studies, from the earliest study planning stages through the final analysis, represents a paradigm shift over past decades. We believe that this collaboration offers multiple benefits to improving epidemiology studies and risk estimation. In particular, it ensures that doses used to derive risk estimates

are appropriate for the task and were estimated with a clear understanding as to their purpose.

Understanding and characterizing the uncertainty of estimated doses cannot be ignored even though, on occasion, extensive uncertainty analysis has not changed epidemiological conclusions. For reasons of credibility, and to allow for innovations in correcting for distortion of the dose–response function, uncertainty estimation remains a priority.

Improvements in previously used dose estimation tools, e.g. phantoms of the human body and computer simulation methods, will benefit dosimetric estimation and related epidemiological studies. Continued development and improvement of such tools should be encouraged. The development of new dosimetric tools, e.g. inexpensive biodosimetry methods with low detection limits, would enable verification or modification of model-based dose estimates.

The National Cancer Institute, having taken note of the relative void in the literature on how to apply dosimetry to improve epidemiological studies, undertook preparation of this special issue to share new knowledge and to encourage further development of these concepts. We anticipate that the measure of our success will be seen over the next 20 years when studies now only being contemplated are completed and bear some fruit of these developmental efforts.

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